

Morbidity and Mortality of Bloodstream Infections in Patients With Severe Burn Injury – A Matched Cohort Study

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Abstract (word count: 250)

Objective: To evaluate the effects of bloodstream infections [BSI] in patients with severe burn injuries.

Methods: Retrospective (1992-2006), pairwise-matched (ratio 1:1 to 1:2), risk-adjusted cohort study in a 6-bed burn unit. A comparison was made between ‘exposed’ patients with microbiologically documented BSI (n=76) and non-exposed subjects (n=103) matched on burn severity (identical Belgian Outcome in Burn Injury [BOBI] score) and length of hospitalization (equivalent or longer than the time-to-event in the exposed patient). Main outcome measures were length of hospitalization and mortality.

Results: Predominant pathogens were *Staphylococcus aureus*, enterococci, *Pseudomonas aeruginosa*, *Escherichia coli*, coagulase-negative staphylococci, and *Candida* spp. Median age was 42 years (interquartile range [IQR] 31-52y). Median total burned surface area was 40% (IQR: 25-50%). Fifty-four percent experienced an inhalation injury. The median BOBI score was 4 (IQR: 2-5). The median ICU stay before onset of bacteremia was 11 days (IQR: 5.3-19.8d). Appropriate antimicrobial therapy was initiated within the first 48h in 76.3%. The exposed group had a higher need for vasopressive/inotropic support (57.9% vs. 39.8%, $p=0.017$), whereas need for ventilatory assistance and renal replacement therapy were not significantly higher. Hospital mortality did not differ (11.8% vs. 17.5%, $p=0.298$). However, BSI was associated with an additional length of hospitalization of 25 days (61 vs. 36d; $p<0.001$), and an excess length of mechanical ventilation of 11 days (21 vs. 10d; $p<0.001$).

Conclusions: In this cohort of burn patients, BSI did not adversely affect survival, but contributes to a substantial economic burden through excess length of ventilator dependency and hospital stay.

Introduction

Advances in burn care substantially improved the outcome of patients with severe burn injuries over the past decades¹. Following better acute phase survival, infectious complications became more prominent, with bloodstream infection (BSI) among the most prevalent²⁻⁵. Burn patients are at high risk for BSI because of large skin defects. The odds of BSI increase with burn size and depth⁴. Early debridement and wound closure is advocated to decrease infection risk, but even then colonisation of burns is difficult to avoid, potentially leading to systemic invasion⁶⁻⁸. Furthermore, burn patients are at risk for BSI because of the use of invasive devices, multiple surgical procedures, and prolonged hospitalization. Based on single center data from a 9-year period, Bang et al. reported a 23.5% mortality among 166 burn patients with BSI⁹. In an earlier study these investigators also demonstrated BSI to be a dominant cause of death¹⁰. In burn patients with *Stenotrophomonas maltophilia* BSI, a 31.7% mortality was found¹¹. A study addressing burned US military casualties, reported BSI to be associated with a 2.6-fold risk of death¹². As such, fatality rates associated with BSI in burn victims have been estimated between 20-30%. However, as BSI generally occurs in more severely burned patients it is difficult to distinguish mortality due the infection from mortality due to general trauma severity. Hence, matched cohort designs may be advocated to assess the clinical impact of BSI¹³. A mortality of 31% was reported in 29 burn patients with *Acinetobacter baumannii* BSI, compared to a 14% mortality in matched non-exposed patients¹⁴. Also by a matched cohort study, Vinsonneau et al. demonstrated a significantly higher mortality in candidemic burn patients compared to non-exposed patients (30.0% vs. 7.8%)¹⁵. As far as we know no study assessed the attributable mortality of BSI in general (including all pathogens) in a burn population. Therefore the objective of this study was to evaluate morbidity and mortality of BSI in severely burned patients by means of a

matched cohort study that provides as adequate as possible adjustment for burn related mortality.

Methods

Setting. This study was conducted in the burn unit of [blinded]. The unit serves a geographic area of ~2,608,000 inhabitants. Approximately 60–80 patients are admitted to the unit yearly. Our total burn population has a median TBSA of 13%, median age of 30y, approximately 12% inhalation injury, a median length of stay of 12 days, and 7% mortality [reference blinded].

The unit has six separate isolation rooms equipped with a shower and bath. Intensivists from the surgical ICU and plastic surgeons are responsible, respectively, for intensive care and wound care. We use a mixed crystalloid-colloid scheme for fluid resuscitation. In the 1980s human albumin was used as colloid; since the 1990s semisynthetic colloids such as starches and gelatin solution have been used. We start at a hourly dose of 2 ml/kg per 1% burned surface area. On the first day one-half of the calculated fluid requirement is administered within the first 8 h following the burn, and the other one-half over the following 16 h. In the first 24 h after the burn one-third of the total fluid volume consists of colloids colloids and the other two-thirds of hypertonic saline (1 l NaCl 0.9% + 50 mEq NaHCO₃). During the second 24-h period colloids comprise two-thirds of the total fluid volume. Volume resuscitation is guided by urine output and hemodynamics. Early enteral nutrition has been the practice in our unit since 1998. Patients during the period 1985–2001 were showered on a daily basis with chlorexidine solution while during the last 2 years of the study period a betadine solution was used. Partial thickness burns were covered with silver sulfadiazine from 1985 to 1998; thereafter hydrocolloid dressings have been used. Full thickness burns are covered with cerium nitrate–silver sulfadiazine. Early excision of burn wounds has never been the practice in our burn unit. The use of polarized light to stimulate wound healing in partial thickness burns was introduced in our unit for scientific purposes in 1996. Since 1998 all partial thickness burns are treated with polarized light limiting the need for surgery to full thickness

burns and difficultly healing deep dermal burn wounds. Twice weekly microbiological monitoring indicates the patient's colonization status. No antibiotic prophylaxis is used.

Design. A retrospective, pairwise-matched (matching ratio 1:2 or 1:1 if not feasible), risk-adjusted cohort study was performed with 'exposed' patients admitted to the burn unit between 1992-2006 whose developed microbiologically documented BSI. Non-exposed patients were selected from a database including all burn patients admitted to the unit. The study was approved by the Ethics Committee at [blinded].

Case finding. A prospective, case-based and laboratory-based surveillance program of BSI by the infection control team was used for the retrospective search for all burn patients with BSI. Registration of BSI started from blood cultures yielding a microorganism, with subsequent ad hoc determination of clinical significance, and presumed or definite inciting focus of infection by mutual agreement between the attending intensivist, infectiologist and microbiologist. In case of multiple episodes, only the first BSI episode was considered.

Matching procedure. The purpose of matched cohort studies is to achieve reliable estimates of attributable mortality through accurate adjustment for confounding covariates. Hence, strict matching on prognostic factors is pivotal^{13,16-21}. Therefore, exposed patients were matched with non-exposed patients with an identical Belgian Outcome in Burn Injury (BOBI) score²². This 10-point scale classification considers three major risk factors for mortality: age, total burned surface area (TBSA), and inhalation injury^{22,23}. It divides age and TBSA in respectively 4 (0 to 3 points) and 5 (0 to 4 points) risk categories, and if present, inhalation injury scores three additional points. This matching procedure resulted in an equal *a priori* expected mortality and allows to assess the impact of a subsequent complication. Non-exposed patients were selected within a 5-year timeframe before or after the admission year of the index BSI-patient. Non-exposed patients were required to have a 'time-to-discharge' at least equal to the 'time-to-event' in the corresponding exposed patient¹⁷. Selection of non-

exposed patients was made without knowledge of outcome. If there were >2 potential non-exposed, matching was based on the admission date nearest to that of the index exposed patient.

Definitions & outcome measures. Definitions of BSI, determination of BSI sources, methods for antimicrobial susceptibility testing, and appropriate antimicrobial therapy are described elsewhere²⁴⁻²⁶. Antimicrobial resistance is defined^{24,27,28} as resistance to fluconazole for *Candida* species, as resistance to methicillin for staphylococci, as resistance to vancomycin for enterococci, as resistance to ampicillin for streptococci, as production of extended-spectrum Beta-lactamases for *Enterobacteriaceae*, and as resistance to one of the following agents for Gram-negative non-fermenting bacteria: ceftazidime, piperacillin, ciprofloxacin, imipenem or meropenem.

Blood cultures are sampled routinely when patient's temperature rises above 38.4° Celsius or bacteremia is suspected because of hemodynamic instability, chills or new organ failure. They are processed following the BacT/Alert® (Organon Teknika Corp., Durnham, NC) procedure. Susceptibility testing was in accordance with the latest guidelines recommended by the NCCLS or CLSI at any time during the study period.

Clinical outcome evaluation is based on the need for organ support (need for mechanical ventilation, renal replacement therapy, vasopressive/inotropic support) and in-hospital mortality. Excess length of hospitalization and ventilator dependency were used major indicators of added morbidity. The excess length of hospitalization is calculated by subtracting the median length of hospitalization from the non-exposed group from this of the exposed group. As exposed patients were matched on exposure time ('time-to-event' in the exposed vs. 'time-to-discharge' in the non-exposed), the difference in length of stay indicates the added proportion of hospitalization due to the infectious complication¹⁷.

Statistics. Mann-Whitney U and X^2 test were used as appropriate. Relationships with mortality were assessed by logistic regression analysis. The following variables were entered in the regression model, and stepwise removed if $p > 0.1$: age, gender, TBSA, inhalation injury, duration of hospitalisation, BSI, AKI and need for vasopressive support. Hereby odds ratios and 95% confidence intervals (CI) are reported. Covariates with a plausible relationship with mortality or $p < 0.1$ in univariate analysis were included in the model. As BSI was the variable of interest, this variable was kept in the model, irrespective of the associated p-value. All tests were 2-tailed.

Results

Patients with bloodstream infection (exposed cohort). During the 15-year period 1125 patients were admitted to the burn unit. In total, 178 episodes of BSI occurred (prevalence: 15.8/100 admissions) in 76 patients. Forty-three patients had multiple episodes of BSI (on average 3.4 episodes). Table 1 summarizes the causative pathogens involved. In 28% of the episodes, multiple bacteria were found. The median time between admission and onset of BSI was 11 days (IQR 5-20). Fifty-two episodes were primary BSI (39.4%), whereof 23 originated from contaminated catheters (n=23, 17.5%). The burn wound was the main source of secondary BSI (n=35, 26.6%). In 58 patients appropriate antibiotic therapy was initiated within 48 hours. In-hospital mortality was 11.8% (n=9), and 9.1% (n=5) when the first episodes was with a single pathogen. Of the patients with a poly-microbial first episode, 19% died (n=4).

Matched cohort. Matching was successful for all patients, but for 42 exposed patients only one suitable non-exposed subject was found. So, the matching procedure resulted in a matched cohort study with 76 exposed and 103 non-exposed subjects. Table 2 summarizes the characteristics of the exposed and non-exposed groups. Compared to non-exposed subjects, patients with BSI had a higher need for vasopressive/inotropic support, whereas need for ventilatory assistance and renal replacement therapy were not significantly higher among exposed patients. Hospital mortality did not differ between both groups. However, BSI was associated with an additional length of hospitalization of 25 days (61 vs. 36d), and an excess length of mechanical ventilation of 11 days (21 vs. 10d). Logistic regression analysis confirmed that BSI did not affect survival (table 3).

Discussion

In this cohort, BSI did not contribute to mortality, but caused additional morbidity, as evidenced by the higher need for vasopressive/inotropic agents, a prolongation of ventilator dependency and hospitalisation. The absence of attributable mortality in patients with BSI was confirmed by multivariable regression analysis. Instead, older age, higher TBSA, renal replacement therapy and need for vasopressors/inotropics were identified as risk factors for mortality. Strangely enough inhalation injury, a factor strongly compromising prognosis in other studies^{1,29-31}, was not associated with death. Probably inhalation injury contributes more to early deaths, while the present cohort generally includes acute phase survivors prone to late-onset infectious complications.

In contrast with previous reports^{9,10,14,15}, our study illustrates that, once adjusted for prognostic covariates, BSI does not necessarily impede survival in burn victims. Absence of excess mortality^{24,25,32-35}, as well as dramatic attributable mortality rates have been demonstrated before in bacteremic critically ill patients^{15,19,36,37}. The likelihood of survival depends on unchangeable characteristics such as severity of disease, causative pathogen, antimicrobial resistance, and patient age^{12,13,38-40}. Essential to optimize the odds of survival is prompt initiation of appropriate therapy^{3,41-43}, which was 76.3% in our study. Yet, mortality in patients not receiving appropriate therapy within the critical time frame of 48h was not worse (12.1% vs. 11.1% in patients receiving appropriate therapy). A possible reason might be that mostly BSI caused by (methicillin-resistant) coagulase-negative staphylococci, known as low virulence pathogens, were treated inappropriately. Anyhow, insufficient study-power hampers this particular analysis.

As matched cohort studies are prone to selection and survival bias^{13,17,44}, reliability of the non-exposed group is crucial. To avoid survival bias non-exposed patients were required to have a time-to-discharge at least as long as the time-to-event in the exposed patient (=onset BSI).

Additionally, we matched subjects based on the BOBI score as this classification summarizes the most powerful prognostic indicators^{22,23}. An advantage of this matching procedure is that the validity of the non-exposed group can be judged by comparing the observed and expected mortality rates. In our study, the observed mortality of the non-exposed group (17.5%) was situated within the 95% CI of the expected mortality (14.7-30.9) indicating a reliable non-exposed group with an outcome in line with the expectations. Percentages TBSA differ statistically, but the clinical relevance of the observed difference (30% vs. 40%) is of minor clinical relevance as mortality associated with percentage TBSA only starts to incline substantially from more than 40% as indicated by Ryan et al⁴⁵. Also in the BOBI score a TBSA ranging 21% to 40% corresponds with 1 point. Therefore exposed and non-exposed patients might have different percentages of TBSA while having an equal BOBI score, and hence have similar outcome predictions. As such, the observation that TBSA was significantly lower among the non-exposed is overruled by the equal BOBI scores.

A disadvantage of this study is the single-centre design. Nevertheless, the homogenous standard of care used for both exposed and non-exposed patients, is an advantage of this single-centre approach. Another potential weakness is that exposed patients were recruited from a substantial time period in which favorable evolutions in survival have been observed¹. We try to counter this problem by selecting non-exposed based on year of admission, but a 5-year frame was necessary to match all exposed patients. This may be borderline acceptable as survival improved over time per 5-year period (OR 0.73, 95% CI: 0.56-0.94)¹.

In conclusion, in this cohort of burn patients BSI did not adversely affect survival. BSI was, however, associated with a significant excess in duration of mechanical ventilation and hospitalization, thereby representing a substantial economic burden. These data underscore the need for vigorous application of evidence-based, cost-effective preventive measures.

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Table 1 - Microorganisms involved in 76 episodes of bloodstream infection in patients with severe burn injuries (only first episode is included)

Microorganism	n episodes (%)	n episodes with single isolated pathogen (%)	n antimicrobial resistant pathogens (%) ^a
Gram-positive bacteria (46 isolated pathogens)	41 (53.9)	21 (45.7)	14 (30.4)
Coagulase-neg staphylococci	12 (15.8)	8 (66.7)	9 (75.0)
<i>Staphylococcus aureus</i>	14 (18.4)	10 (71.4)	4 (28.6)
Enterococci	14 (18.4)	2 (14.3)	-
Streptococci	6 (7.9)	1 (16.7)	1 (16.7)
Gram-negative bacteria (45 isolated pathogens)	42 (55.3)	26 (57.8)	9 (20.0)
<i>Enterobacter</i> species	9 (11.8)	6 (66.7)	3 (33.3)
<i>Pseudomonas aeruginosa</i>	12 (15.8)	6 (50.0)	1 (8.3)
<i>Sphingobacterium meningosepticum</i>	1 (1.3)	1 (100)	1 (100)
<i>Klebsiella</i> species	7 (9.2)	2 (28.6)	1 (14.3)
<i>Acinetobacter baumannii</i>	3 (3.9)	3 (100)	3 (100)
<i>Escherichia coli</i>	12 (15.8)	8 (66.7)	-
<i>Serratia marcescens</i>	1 (1.3)	-	-
<i>Candida</i> species (10 isolated pathogens)	10 (13.2)	8 (80.0)	-
Total (101 isolated pathogens):	76 (100)	55 (54.5)	23 (22.8)
→ Polymicrobial bloodstream infections	21 (27.6)	-	3 (6.5)

^aAntimicrobial resistance is defined as resistance to fluconazole for *Candida* species, as resistance to methicillin for staphylococci, as resistance to vancomycin for enterococci, as resistance to ampicillin for streptococci, as production of extended-spectrum Beta-lactamases for *Enterobacteriaceae*, and as resistance to one of the following agents for Gram-negative non-fermenting bacteria: ceftazidime, piperacillin, ciprofloxacin, imipenem or meropenem.

Table 2 - Characteristics of patients with severe burn injuries and a bloodstream infection (BSI)('Exposed') and matched non-exposed patients

Characteristics	Exposed group (n=76)	Non-exposed group (n=103)	p
Age (years)	42 (31-52)	41 (23-68)	0.911
Gender, % male	65.8	67.0	0.866
Total burned surface area (TBSA), %	40.0 (25.3-50.0)	30.0 (13.0-47.0)	0.005
Inhalation injury	41 (53.9)	54 (52.4)	0.840
BOBI score ²²	4 (2-5)	4 (2-5)	0.913
BOBI score-related expected mortality, %	20.0 (5.0-30.0)	20.0 (5.0-30.0)	0.913
Time-to-event/Time-to-discharge, days ^a	11 (5-20)	31 (14-55)	<0.001
Vasopressive/inotropic support	44 (57.9)	41 (39.8)	0.017
Mechanical ventilation	46 (60.5)	57 (55.3)	0.488
Renal replacement therapy	5 (6.6)	2 (1.9)	0.114
Duration of hospitalization, days	61 (42-119)	36 (20-57)	<0.001
Duration of mechanical ventilation, days	21 (16-33)	10 (6-21)	<0.001
In-hospital mortality	9 (11.8)	18 (17.5)	0.298

Data are reported as n (%) of patients or as median value (interquartile range). ^aThe time-to-discharge in the non-exposed group should be at least as long as the time-to-event in the exposed group. Consequently, the a-priori risk to develop BSI is at least as high in the non-exposed group.

Table 3 - Logistic regression analysis to assess the relationship between in-hospital mortality and covariates.

Variable	Odds Ratio	p
	(95% confidence interval)	
Age (/10y increase)	2.01 (1.37-2.95)	<0.001
Total burned surface area (/10% increase)	2.30 (1.61-3.29)	<0.001
Acute kidney injury	24.20 (1.70-344.83)	0.019
Need for vasopressive/inotropic support	3.70 (1.06-12.95)	0.041
Bloodstream infection	0.83 (0.22-3.16)	0.779
Total hospital stay (/day increase)	0.96 (0.94-0.98)	<0.001

Gender and Inhalation injury were stepwise removed from the model, because these variables did not have a significant effect on mortality.